

REMARKS

The present invention is directed to polymorphic forms and solvates of ondansetron hydrochloride. Claims 5-8 and 10-93 are pending.

Discussion of Office Action

In an office action dated July 28, 2004, the Office rejected claims 5-8 and 10-93. The Office objected to claims 5-8 and 10-18.

Amendments to the Claims

Claims 8, 10, and 16 are amended to correct the dependency.

Claims 49-50, 52-53, 57-58, 67, 74-76 are amended to eliminate the language "and hydrates thereof."

Claims 23, 24, 40, 42, 44, 71, 92, and 93 are canceled to limit the issues for allowance or possible appeal.

35 U.S.C. § 112 Rejection

Enablement

Claims 23, 40, 42, 44, 71, 89-91, and 93 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In order to limit the issues for possible allowance by the Examiner or for appeal, the Applicants have canceled claims to pharmaceutical compositions/methods of treatments (23, 24, 40, 42, 44, 71, 92 and 93), and have amended claims 89-91 so that these claims are no longer directed to pharmaceutical compositions. Therefore, the rejection is moot.

Indefiniteness

Claims 45 and 66

Claims 45 and 66 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the claims are indefinite because they are directed to the anhydrous ondansetron hydrochloride compound, but it contains water. In regard to claim 45, as described by the specification at page 9, lines 1-9, "the water absorbed by the crystal is not within the crystal," *i.e.*, the water is not a "hydrate water." It is generally known in the art that an anhydrous form may absorb up to 2% water without becoming a hydrate since the water absorbed is not incorporated into the crystal structure, but remains outside of the crystal structure.

In regard to claim 66, the specification discloses that the form is an isopropanolate that may contain water. There is no teaching in the specification that Form E is anhydrous.

Claim 92

Claim 92 has been canceled to limit the issues for allowance or possible appeal.

35 U.S.C. § 102 Rejection

Claims 19-23, 39-45, 49-50, 52, 57-58, 62-67, 71, 74-76, 87-91, and 93 were rejected under 35 U.S.C. § 102 as being anticipated by Wu Gousheng et al. (CN 1113234).

In order for a claim to be anticipated under 35 U.S.C. § 102, a single prior art reference must disclose each and every element of the claim in exactly the same way. *See* MPEP § 2131.

Claims 19-23 and 39-45 recite anhydrous ondansetron hydrochloride. Wu Gousheng discloses a monohydrate form (embodiments A₁ and A₂) and a dihydrate form (embodiment B), but it does not describe an anhydrous form. The anhydrous form, unlike the monohydrate and dihydrate forms, does not have a water molecule *within* the crystal structure. Thus, even with respect to the anhydrous forms with a specified water content, Wu Gousheng is not anticipatory because it only discloses crystalline forms with water *within* the crystal structure, *i.e.*, the monohydrate and dihydrate forms.

Claims 49-50 recite ondansetron hydrochloride Form C. Claim 52 recites ondansetron hydrochloride Form D. Claims 57-58 and 66 recite ondansetron hydrochloride Form E. Claim 67 recites ondansetron hydrochloride Form H. Claims 74-76 and 93 recite ondansetron hydrochloride Form I. The claims have been amended to eliminate the language “and hydrates thereof”. Wu Gousheng does not disclose any of the claimed polymorphic forms. As described in Applicants’ Response to Office Action dated July 7, 2003, each of the claimed forms has a powder X-ray diffraction pattern that is different from that of the Wu Gousheng product. (See Response pp. 10, 11, 12, 13-14, 15). The detailed comparison of X-ray powder diffraction peaks that was presented by Applicants refutes the Examiner’s

statement that the X-ray diffraction patterns are “inherently present” in the Wu Gousheng compound. (Office Action p. 5).

Claims 62-66 recite isopropanolate forms of ondansetron hydrochloride. Wu Gousheng does not disclose an isopropanolate form of ondansetron hydrochloride. In fact, Wu Gousheng does not disclose the use of isopropanol for any purpose. (See Applicants’ to Office Action dated July 7, 2003, p. 13). Because Wu Gousheng fails to disclose each and every element of the claims, Wu Gousheng is not anticipatory.

Dependent claim 71 is not anticipated at least for the reasons set forth above for claims 49, 50, 52, 57, 58, and 62-67.

Claims 87-91 recite ondansetron hydrochloride with a small particle size. Wu Gousheng is silent regarding particle size. As described in Applicant’s Response to Office Action dated July 7, 2003, MPEP § 2131.01 requires that such a gap in the reference must be bridged using extrinsic evidence. The Examiner has produced no extrinsic evidence to support the bald assertion that the claimed “range of particle size” is “inherently present” in the Wu Gousheng compound. (Office Action p. 5).

35 U.S.C. § 103 Rejection

Claims 5-8, 10-20, 23-48, 51, 53-56, 59-65, and 68-93 were rejected under 35 U.S.C. § 103(a) as being obvious in view of Wu Gousheng et al. (CN 1113234). The rejection is moot for canceled claims 23, 24, 40, 42, 44, 71, 92, and 93.

To establish *prima facie* obviousness, the prior art references, when combined, must teach or suggest all the claim limitations, there must be some suggestion or motivation to combine the reference teachings, and a reasonable expectation of success. MPEP § 2143.

Claims 5-7 recite a process for preparing ondansetron hydrochloride monohydrate by contacting ondansetron hydrochloride dihydrate with an ethanol:water mixture. Even though the ondansetron hydrochloride monohydrate product is known, nothing in the Wu Gousheng reference suggests the Applicants’ claimed route of synthesis. Wu Gousheng discloses a method of preparing the monohydrate by vacuum dehydration of the dihydrate under vacuum over P₂O₅. Respectfully, the Examiner has failed to establish a *prima facie* case of obviousness because Wu Gousheng does not teach or suggest the claim limitation of an ethanol:water mixture. The Examiner refers to p. 8, lines 19-24 as support for “a

water/alcohol solvent,” but the reference merely describes elution with aqueous HCl and then water. This general procedure does not disclose “a water/alcohol solvent” as asserted by the Examiner.

Claim 8 recites a process for preparing ondansetron hydrochloride dihydrate by hydrating the monohydrate under at atmosphere of 50% relative humidity or greater. The Examiner concedes that Wu Gousheng does not suggest the limitations of step b of claim 8. (Office Action Sept. 24, 2003, p. 7, 9).

Claims 10-18 recite a process for preparing ondansetron hydrochloride Form A containing between about 5% water and 10% water. As 5% water is the monohydrate content and 10% water is the dihydrate water content, the product may contain an intermediate degree of hydration between the monohydrate and the dihydrate. Wu Gousheng does not teach or suggest a product having an intermediate degree of hydration nor does it teach or suggest any process for making such a product.

Claims 25-38, 46-48, and 82-86 recite processes for preparing Form B. Claims 39, 41, 43, and 45 relate to Form B. Claim 51 recites a process for preparing Form C. Claims 53-56 recite processes for preparing Form D. Claims 59-65 relate to Form E and processes for preparing Form E. Claims 68-70 recite processes for preparing Form H. Claims 72-81 relate to Form I and processes for preparing Form I. Wu Gousheng does not teach or suggest any of these polymorphs, nor any processes for preparing them. The disclosure of one solid state of ondansetron hydrochloride does not motivate a skilled artisan to prepare another, as yet unknown polymorph. Even if one of skill in the art were motivated by some general desire, there is no predictability that one of skill in the art would find a new polymorph, nevertheless these particular polymorphs.

Furthermore, Wu Gousheng does not teach or suggest the use of particular claimed solvent systems, *e.g.*, toluene, xylene, ether, etc. The Examiner assumes that the solvent systems disclosed in Wu Gousheng are similar in functionality to the claimed solvent systems. (Office Action p. 8). But because the prior art solvent systems and the claimed solvents systems yield different products, they must necessarily function differently. (See Applicants’ to Office Action dated July 7, 2003, p. 20).

Claims 87-91 recite ondansetron hydrochloride with a small particle size. The Examiner has failed to establish a *prima facie* case of obviousness because the reference does not teach or suggest the particle size limitation of these claims.

Applicants respectfully request that the obviousness rejection be withdrawn.

Claim Objections

Claims 5-8 and 10-18 were objected to as dependent on rejected claims.

Claim 5 was amended in Applicants' Response to Final Office Action dated March 19, 2004. Claim 5 was rewritten in independent form. Accordingly, Applicants respectfully request that this objection be withdrawn for claim 5, as well as claims 6 and 7 which depend from claim 5.

Claims 8, 10, and 16 are currently rewritten in independent form. Accordingly, Applicants respectfully request that this objection be withdrawn for claims 8, 10, and 16, as well as dependent claims 11-15 and 17-18.

Correction of the File History

In the Office Action Summary, the Examiner writes that the Non-final Office Action is responsive to communications filed on May 12, 2004. However, Applicants did not file any communications on that date. The PAIR system which purports to be the official record lists the following communications, none of which were filed by Applicants:

05-20-2004	Date Forwarded to Examiner
05-12-2004	Request for Continued Examination (RCE)
05-20-2004	Express Abandonment (for Entry of CPA / RCE / Rule129)
05-12-2004	Request for Extension of Time – Granted

Applicants discussed this matter with the Examiner and the Supervisory Examiner on November 29, 2004. Examiner Oh stated that his personal file matches Applicants, that is, it does not contain any filings by the Applicants in May 2004. The Supervisory Examiner Tsang believes the discrepancy in the file history is due to a scanning problem. She contacted the scanning department, but has not yet been able to resolve the problem.

Appl. No. 10/016,752
Amdt. dated Jan. 27, 2005
Reply to Office Action of July 28, 2004

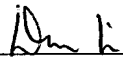
Applicants respectfully request that the erroneous filings be removed from the official file history of this application.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is invited to telephone the undersigned at the number below. The undersigned may also be contacted by email at dziker@kenyon.com.

Respectfully Submitted,

Date: January 27, 2005



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